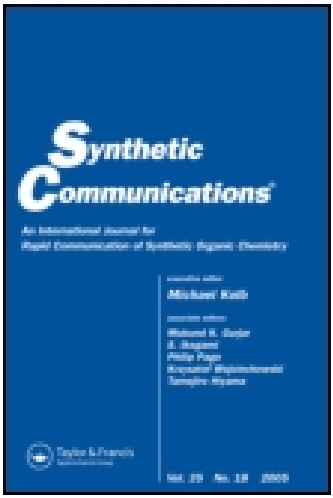

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The Reaction of Enaminones with Grignard Reagents: Synthesis of α,β-Unsaturated Ketones

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THE REACTION OF ENAMINONES WITH GRIGNARD REAGENTS: SYNTHESIS OF α,β-UNSATURATED KETONES

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Abstract: Enaminones in toluene react with Grignard reagents in tetrahydrofuran at 0-25 °C, to give selectively and with high yields the corresponding α,β-unsaturated ketones.

The α,β-unsaturated carbonyl compounds are amongst the most important intermediates and one useful for many synthetic purposes.[1] Furthermore, this bifunctional moiety is present in a large number of molecules of biological relevance. The problems associated with the preparation of such compounds have been well documented[2] and some particularly efficient methods have been developed for their preparation. We report here our results concerning the preparation of cyclic and aliphatic α,β-unsaturated ketones, by reaction of enaminones dissolved in toluene with Grignard reagents in tetrahydrofuran (THF).

Results and discussion

During the course of our studies related to the synthesis of highly soluble polypyridines, we were found the need to prepare substantial quantities of the α,β-

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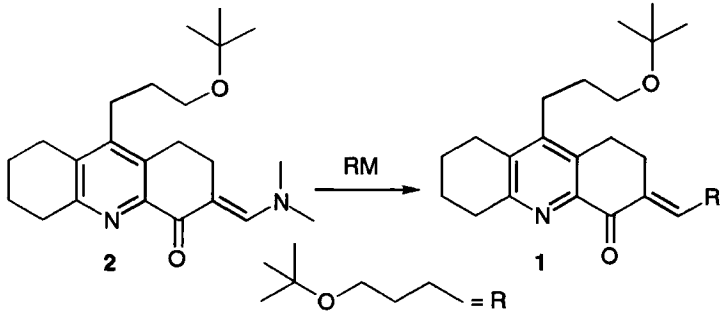
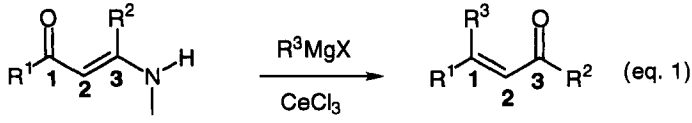
unsaturated ketone **1**.[3] Abdulla and co-workers[4] have reported what appeared to be the most attractive method. They prepared α,β-unsaturated compounds in good yields by alkylation of enaminones with organolithium species through a formal nucleophilic substitution of the amino fragment by the organometallic residu. In our case, the reaction of the 3-(2,2-dimethyl ethoxy) propyllithium **3a** with the enaminone **2**[3], which was chosen as an example for the initial study, gave in THF at -30 °C the desired compound **1** (Scheme 1) in unsatisfactory yields (~30%).

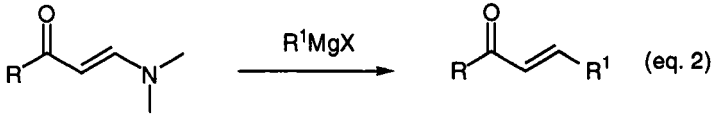


Scheme **1**

This disappointing result prompted us to investigate the alkylation of enaminone derivatives with Grignard reagents. Recently the preparation of α,β-unsaturated ketone by reaction of Grignard reagents with enaminones in the presence of cerium has been described (eq. 1).[5] With aliphatic ketones this procedure gave high yields of β-disubstituted α,β-unsaturated ketone *via* 1,2-addition resulting in 1,3-carbonyl shift and this was not applicable to cyclic ketones.



In fact, the reaction of Grignard reagents with enaminones for the syntheses of aliphatic α,β-unsaturated ketones was even earlier described, but the yields were not satisfactory and the method was not generalised (eq. 2).[6]

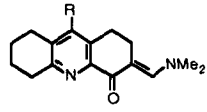
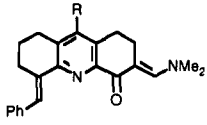
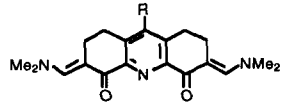
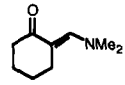
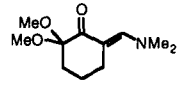
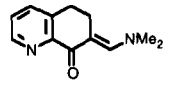
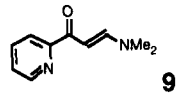


(eq. 2)

When the reaction of the enaminone **2** with the 3-(2,2-dimethyl ethoxy) propylmagnesium chloride **3b**[7] (Scheme 1) was carried out in THF at -30 °C[4] the desired product **1** was obtained in poor yield (15%). At room temperature this reaction in THF affords higher yields up to 45%. It is worth pointing out that in this case, the variation of the quantities of the alkylating agent **3b** and the concentration of the mixture, the time of the reaction and the use of co-solvents such as N,N,N',N'-Tetramethylethylenediamine (TMEDA), did not influence the yield of **1**. However, the addition of the solution of the Grignard reagent **3b** in THF to a solution of **2** in dry toluene at 0 °C, followed by stirring for 16h at room temperature, gives after purification, the desired α,β-unsaturated ketones **1** with high yield (90%). The use of mixture of diethyl ether and benzene[6b(5b)] as solvent instead of THF and toluene, yielded the desired product with lower yield (60%).

Having found favourable reaction conditions for the alkylation of the enaminone **2** with the 3-(2,2-dimethyl ethoxy) propylmagnesium chloride **3b**, we turned our attention to testing the applicability of this procedure to other enaminones and Grignard reagents. Condensation of ketones with Bredereck's reagent[8], at 50-100 °C for 1 to 12 h under argon gave the corresponding enaminones in excellent yield (>95%).[9] For example, the reaction of cyclohexanone with 1.05 equivalents of the Bredereck's reagent at 90 °C for 2h gave the enaminone **6** (entry 4) in 98% isolated yield. When the enaminones were treated with 1.25 equivalents of **3b** under the

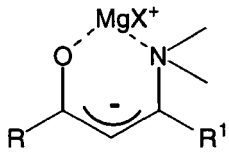
Table 1 : Enaminones alkylation using the described method*

Entry	Enaminone(a)	Grignard(b) RMgCl	Enone(c,d) (Yield %)
(1)	 2	R=$(CH_2)_3OtBu$	1 (90%)
(2)	 4	R=$(CH_2)_3OtBu$	10 (94%)
(3)	 5	R=$(CH_2)_3OtBu$	11 (67%)
(4)	 6	R=$(CH_2)_3OtBu$ R=Me R=nBu R=Ph	12 (80%) 13 (85%) 14 (75%) 15 (85%)
(5)	 7	R=$(CH_2)_3OtBu$	16 (91%)
(6)	 8	R=$(CH_2)_3OtBu$ R=Me	17 (92%) 18 (96%)
(7)	 9	R=$(CH_2)_3OtBu$ R=Me	19 (85%) 20 (79%)

*Notes : (a) enaminones are obtained according to the published procedure[9] using Brederek's reagent (tertiobutoxy bis-*N,N*-dimethylaminomethane), (b) methylmagnesium chloride, phenylmagnesium chloride and n-butylmagnesium chloride were purchased. 3-(2,2-dimethyl ethoxy) propylmagnesium chloride is obtained in two steps from 3-chloro propane 1-ol, (c) isolated yield after purification (column chromatography or distillation), (d) all intermediates and products gave satisfactory spectral analysis.

experimental conditions described for **1**, the corresponding α,β-unsaturated ketones were obtained with good to excellent yields. The generality of this process is demonstrated by successful extension to methyl magnesium, *n*-butyl magnesium and phenyl magnesium reagents. Using these conditions, the akylation reactions, between 0-25 °C are very clean and the α,β-unsaturated compounds are obtained, after purification, in good to excellent yields. The results are summarised in the Table **1**. With the enaminone **6**, the reaction with different Grignard reagents, gave under the conditions described above, the products **12**, **13**[2d], **14**[4] and **15**[4] in high yield. In the case of the *bis*-enaminone **4** which is not very soluble in toluene at 0 °C, the alkylation was carried out with 4 equivalents of the Grignard reagent **3b** in the mixture of PhMe/THF at room temperature, and the product was purified by column (deactivated alumina; ethyl acetate/n-pentane; 8:2).Nevertheless, the preparation of the ketal enone **16** was accomplished by the reaction of **3b** with the enaminone **7**[10] in the mixture of PhMe/THF at 0 °C and the desired product **16** was purified by chromatography on deactivated alumina (ethyl acetate).

The high yields obtained with our procedure is an illustration of a strong solvent effect involved in this reaction. On the other hand the desired α,β-unsaturated ketones were obtained without formation of secondary products coming from a further attack by the Grignard reagents. According to this observation we assume that alkylations take place *via* intermediates such as **21** which have no propensity for additional attack by nucleophiles.[4]



21

In conclusion, this procedure provide a useful route for the synthesis of different α,β-unsaturated ketones.

Typical procedure

*** 9-(3-(2,2-dimethyl ethoxy) propyl) 3-(4-(2,2-dimethyl ethoxy) butylidene) 1,2,5,6,7,8-hexahydro 4-oxo acridine (1).**

3.83g (10.4mmol) of the enaminone **2** dissolved in 30ml of dry toluene is cooled to 0°C under argon. 25ml (12.5mmol, 1.25eq) of a 0.5M solution of 3-(2,2-dimethyl ethoxy) 1-propyl magnesium chloride in tetrahydrofuran was added. Then, the solution was stirred overnight at room temperature under argon. The reaction mixture was concentrated under reduced pressure to dryness and the solid residue dissolved in 150ml of dichloromethane and hydrolyzed with 250ml of water under vigorous magnetic stirring. Solid sodium bicarbonate was added to separate the two phases. The aqueous layer was then extracted twice with 100ml of dichloromethane. The organic layers were combined and were washed successively with saturated sodium bicarbonate, water and saturated sodium chloride and then dried. Finally the solvent was removed and the product was purified by flash chromatography on silica gel (ethyl acetate). 4.13 g (90%) of analytically pure **1** was obtained as a yellow oil.

$C_{28}H_{43}NO_3$: C:75.86% (calc.76.15) H:10.30% (calc.9.89) N:3.06% (calc.3.17) O:10.79% (calc.10.87).^{1}H NMR (250 MHz, $CDCl_3$, δppm/TMS) 6.95 (t, J = 8.4 Hz, 1H), 3.74 (m, 2H), 3.56 (tt, J = 6.3 Hz, 2H), 3.38 (m,4H), 3.04 (s,2H), 2.93 (m, 2H), 2.85-2.70 (m, 6H), 2.36 (q, J = 8.4 Hz, 2H), 1.80-1.60 (m, 8H), 1.22 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 186.5, 156.7, 147.6, 139.6, 135.5, 135.2, 134.3, 72.5, 72.3, 60.6, 60.3, 33.3, 29.4, 29.2, 27.3, 26.1, 24.7, 24.1, 22.5, 22.4. IR 1684cm^{-1}, 1622cm^{-1} (νCO). MS (DCI/NH_3) m/z: 442 [MH^+].

10 was obtained, after purification by column chromatography on deactivated alumina (ethyl acetate), as a yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$, δppm/TMS) 8.14 (s, 1H), 7.48 (m, 4H), 7.28 (d, 1H), 7.00 (t,1H), 3.43 (t,2H), 2.98 (m, 2H), 2.83 (m, 2H), 2.34 (q, 2H), 1.87 (m, 2H), 1.76 (m, 2H), 1.69 (m, 2H), 1.24 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 186.6, 152.2, 147.7, 146.8, 139.9, 137.9, 136.2, 135.3, 134.4, 129.6, 128.0, 127.8, 126.4, 72.6, 72.4, 60.7, 60.3, 29.5, 27.5, 26.6, 25.0, 24.8, 24.4, 22.5. IR 1687cm^{-1}, 1623cm^{-1} (νCO).
MS (DCI/NH_3) m/z: 530 [MH^+].

11 was obtained, after purification by column chromatography on deactivated alumina (ethyl acetate/n-pentane, 80:20), as a yellow oil.
$C_{36}H_{55}NO_5$: C:74.20% (calc.74.31) H:9.33% (calc.9.53) N:2.34% (calc.2.41) O:14.13% (calc.13.75). ^{1}H NMR (250 MHz, $CDCl_3$, δppm/TMS) 6.94 (t, 2H), 3.35 (t, 2H), 3.29 (t, 4H), 2.97 (t, 4H), 2.76 (m, 6H), 2.27 (q, 4H), 1.65 (m, 6H), 1.23 (s, 9H), 1.21 (s, 18H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 185.3, 148.7, 148.4, 140.8, 140.2, 134.4, 72.5, 72.3, 60.2, 60.1, 29.5, 29.3, 27.3, 27.2, 25.2, 24.9, 24.7, 24.6, 24.2. IR 1687 cm^{-1} (νCO).
MS (EI) m/z (% relative intensity): 168 (83), 57 (100).

16 was obtained, after purification by column chromatography on deactivated alumina (ethyl acetate), as a yellow oil.
$C_{16}H_{28}O_4$: C:67.53% (calc. 67.57) H:10.04% (calc. 9.92) O:22.43% (calc. 22.50). ^{1}H NMR (250 MHz, $CDCl_3$, δppm/TMS) 6.51 (t, 1H), 3.37 (t, 2H), 3.22 (s, 6H), 2.50 (t, 2H), 2.22 (m, 2H), 2.08 (t, 2H), 1.68 (m, 2H), 1.18 (s, 9H).
^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 195.0, 139.3, 137.3, 98.4, 72.4, 60.3, 49.0, 32.3, 29.2, 27.3, 26.0, 24.7, 19.5. IR 1709 cm^{-1} (νCO).

17 was obtained, after purification by column chromatography on silica gel (ethyl acetate/methanol, 90:10), as a yellow oil.

$C_{17}H_{23}NO_2$: C:74.29% (calc.74.69) H:8.68% (calc.8.48) N:5.22% (calc.5.12) O:14.27% (calc.11.17). ^1H NMR (250 MHz, $CDCl_3$, δppm/TMS) 8.69 (d, 1H), 7.63 (d, 1H), 7.38 (dd, 1H), 6.98 (m, 1H), 3.38 (t, 2H), 3.00 (t, 2H), 2.82 (t, 2H), 2.37 (m, 2H), 1.73 (m, 2H), 1.18 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 185.7, 149.0, 141.3, 139.6, 136.8, 134.8, 126.3, 72.3, 60.3, 29.3, 27.8, 27.3, 24.8, 24.6. IR 1687cm^{-1}, 1622cm^{-1} (νCO).
MS (DCI-NH_3) m/z: 274 [MH^+].

18 was obtained, after purification by column chromatography on silica gel (ethyl acetate/methanol, 90:10), as a yellow oil.
$C_{11}H_{11}NO$: C:76.08% (calc.76.28) H:6.52% (calc.6.40) N:7.89% (calc.8.09) O:9.51% (calc.9.24). ^1H NMR (250 MHz, $CDCl_3$, δppm/TMS) 8.72 (d, 1H), 7.67 (d, 1H), 7.39 (dd, 1H), 7.18 (q, 1H), 3.03 (t, 2H), 2.85 (t, 2H), 1.92 (d, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 185.9, 149.2, 139.7, 136.9, 136.6, 135.6, 126.4, 27.9, 24.4, 14.0. IR 1687cm^{-1}, 1623cm^{-1} (νCO). MS (DCI-NH_3) m/z: 174 [MH^+].

19 was obtained, after purification by column chromatography on silica gel (ethyl acetate), as a yellow oil.
$C_{15}H_{21}NO_2$: C:73.03% (calc.72.84) H:8.33% (calc.8.56) N:5.89% (calc.5.66) O:12.77% (calc.12.94). ^1H NMR (250 MHz, $CDCl_3$, δppm/TMS) 8.70 (d, 1H), 8.13 (d, 1H), 7.85 (m, 1H), 7.63 (m, 1H), 7.47 (m, 1H), 7.26 (m, 1H), 3.41 (t, 2H), 2.42 (m, 2H), 1.79 (m, 2H), 1.17 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 189.3, 158.8, 156.9, 154.8, 150.0, 126.5, 124.3, 122.4, 72.4, 60.5, 29.6, 28.9, 27.4. IR 1687cm^{-1}, 1623cm^{-1} (νCO).
MS (DCI-NH_3) m/z: 248 [MH^+].

20 was obtained, after purification by column chromatography on silica gel (ethyl acetate/n-pentane, 15:85), as a yellow oil.

$C_{36}H_{55}NO_5$: C:73.20% (calc.73.45) H:6.42% (calc.6.16) N:9.41% (calc.9.52) O:10.97% (calc.10.87). ^1H NMR (250 MHz, $CDCl_3$, δppm/TMS) 8.68 (d, 1H), 8.07 (d, 1H), 7.84 (m, 1H), 7.63 (m, 1H), 7.46 (m, 1H), 7.20 (m, 1H), 1.92 (d, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm, $CDCl_3$=77.0ppm) 189.4, 154.2, 148.9, 145.1, 137.0, 126.9, 126.1, 18.6. IR 1687cm^{-1}, 1623cm^{-1} (νCO). MS (DCI-NH_3) m/z: 148 [MH^+].

Acknowledgment. *We are grateful to the CNRS for financial support, to the "Ministère de l'Enseignement Supérieur et de la Recherche" and the "Ministère des Affaires Etrangères" for doctoral fellowships (C.F., E.B.).*

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(3) Fontenas C., *Thèse de l'Université Paris-Sud; Orsay; France* **1995**.

(4) Abdulla R.F. and Fuhr K.H., *J. Org. Chem.*, **1978**, *43*, 4248.

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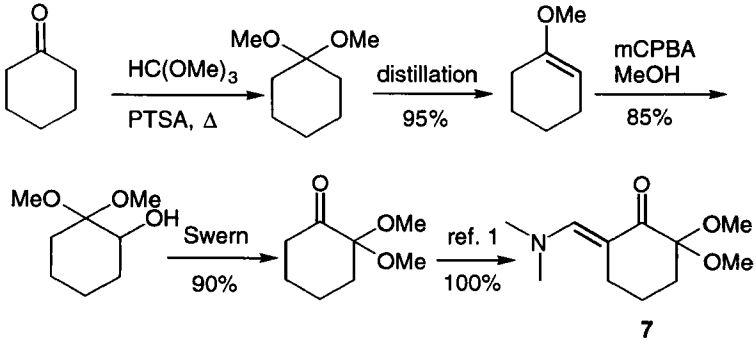
(6) a) Johnson W.S., *J. Am. Chem. Soc.*, **1943**, *65*, 1317; b) Jutz C., *Ber.*, **1958**, *91*, 1867.

(7) Preparation of 3-(2,2-dimethyl ethoxy) propylmagnesium chloride **3b**: A 250ml two-necked flask was charged with 4.84g (200mmol) of magnesium in 20ml of anhydrous THF under an argon flow. To initiate the reaction 0.2ml of 1,2-dibromoethane was added. When the solvent was refluxing, a solution of 10g (66mmol) of 3-(2,2-dimethyl ethoxy) propylchloride and 2ml of 1,2-dibromoethane in 100ml of anhydrous THF were added over 1h. After additional stirring under reflux for 2h, the solution was used immediately.

(8) Brederek H., Effenberger F., Botsh H., Rehn H., *Chem. Ber.*, **1965**, *98*, 1081.

(9) Bejan E., Aït-Haddou H., Daran J.C. and Balavoine G.G.A., *Synthesis*, **1996**, 1012.

(10) The Enaminone **7** was obtained in 4 steps as shown in the Scheme 2.



Scheme **2**

For the first step see: Wohl R.A., *Synthesis*, **1974**, 38. For the second step see: Frimer A.R., *Synthesis*, **1977**, 578. For the oxidation step see:

Mancuso A.J., Swern D., *Synthesis*, **1981**, 165. For transformation of the monoprotected diketone to the corresponding enaminone **7** see ref. 9.

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